THYROID DYSFUNCTION AND INCREASED RISK OF DEVELOPING GESTATIONAL DIABETES MELLITUS

A Dissertation Submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY,

Chennai-600 032

In partial fulfilment of the requirements for the award of the Degree of

MASTER OF PHARMACY
IN
PHARMACOLOGY

Submitted by
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CERTIFICATE

This is to certify that the dissertation work entitled "**Thyroid Dysfunction and Increased Risk of Developing Gestational Diabetes Mellitus"** submitted by University **Regd. No.261525903** is a bonafide work carried out by the candidate under my guidance and submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the Degree of Master of Pharmacy in Pharmacology at the Department of Pharmacology, PSG College of Pharmacy, Coimbatore, during the academic year 2016-2017.

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DECLARATION

I do hereby declare that the dissertation work entitled "**Thyroid Dysfunction and Increased Risk of Developing Gestational Diabetes Mellitus"** submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the Degree of Master of Pharmacy in Pharmacology, was done by me under the guidance of **Mr.G.Venkatesh, M.Pharm.,** at the Department of Pharmacology, PSG College of Pharmacy, Coimbatore, during the academic year 2016-2017**.**

University Reg. No: 261525903

EVALUATION CERTIFICATE

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Examination Center: PSG College of Pharmacy, Coimbatore.

Date:

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Dedicated

To The Supreme Lord

My beloved

Grandmother

&

Parents

ABBREVIATIONS

ATA	**:**	American Thyroid Association
ADA	**:**	American Diabetes Association
ATA	**:**	Anti-Thyroid drugs
AIDS	**:**	Acquired Immunodeficiency Syndrome
ATMs	**:**	Adipose Tissue Macrophages
c AMP	**:**	Cyclic Adenosine Monophosphate
CI	**:**	Confidence Interval
DIPSI	**:**	Diabetes In Pregnancy Study Group India
ESCPG	**:**	Endocrine Society Clinical Practice Guidelines
FT_3	**:**	Free Tri-iodothyronine
FT_4	**:**	Free Thyroxine
FAs	**:**	Fatty Acids
GD	**:**	Grave's Disease
GDM	**:**	Gestational Diabetes Mellitus
GLUT	**:**	Glucose Transporter

HCG	**:**	Human Chorionic Gonadotropin
IHEC	**:**	Institutional Human Ethical Committee
IRS	**:**	Insulin Receptor Substrate
LT_4	**:**	Levothyroxine
OGTT	**:**	Oral Glucose Tolerance Test
PCOD	**:**	Polycystic Ovarian Syndrome
PTU	**:**	Propylthiouracil
PKC	**:**	Protein kinase C
SPSS	**:**	Statistical Package for Social Sciences
SOCS	**:**	Suppressor of Cytokine Signaling
SLE	**:**	Systemic Lupus Erythematosus
TSH	**:**	Thyroid Stimulating Hormone
TFTs	**:**	Thyroid Function Tests
TBG	**:**	Thyroxine Binding Globulin
T3	**:**	Tri-iodothyronine
TRL	**:**	Toll like Receptor

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Chapter 1

Introduction

1. INTRODUCTION

Thyroid disorders are among the common endocrine problems in pregnant women. Thyroid disorders occur when thyroid gland releases more (over active) or less (underactive) thyroid hormones. Thyroid hormone production is regulated by thyroid-stimulating hormone (TSH), which is made by the pituitary gland in the brain (Sahu *et al*., 2010).Thyroid disease affects 2–3% of pregnant women and is associated with adverse pregnancy outcomes. (Abalovich et al., 2007; Fitzpatrick and Russell, 2010; Van Den Boogaard *et al*., 2011).

HYPERTHYROIDISM IN PREGNANCY

When thyroid gland releases more (overactive) thyroid hormones that condition is called Hyperthyroidism. The prevalence of clinical Hyperthyroidism is found in 0.1–0.4% of pregnant women.

Types

Overt hyperthyroidism is seen in nearly 0.002% of pregnancy characterized by a reduced TSH and an increased FT3/FT4 (Brent *et al*., 2007).**Subclinical hyperthyroidism** is seen in 1.7% of pregnancy and is characterized by a suppressed serum TSH and normal FT4(Brent *et al*., 2007)

Causes

Most common cause is Graves' disease. (Bahn *et al*., 2011)other causes of hyperthyroidism in pregnancy include subacute thyroiditis, toxic multinodular goiter, toxic thyroid adenoma and excessive LT4 intake.(Patil-Sisodia *et al*.,2010;Mestman *et al*.,2010)

Complications

If left untreated hyperthyroidism significantly increases the risk of pregnancy and poor fetal outcomes, which includes

- Miscarriage
- Preeclampsia
- preterm birth
- Placental abruption
- Fetal hyperthyroidism (Zimmerman, 1999; Earl *et al*., 2010).

Treatment

According to the Endocrine Society Clinical Practice Guideline (ESCPG) and the American Thyroid Association (ATA), the treatment of choice is with two Anti thyroid drugs (ATDs), MMI and propylthiouracil (PTU), both cross the placenta and hence are used to treat hyperthyroidism. The goal of ATD therapy in pregnant women with hyperthyroidism is to maintain maternal serum FT4 at or just above the upper limit of normal for pregnancy using the smallest ATD dose possible. Propylthiouracil (PTU). (Abalovich et al., 2007; Stagnaro-Green *et al*., 2011).

HYPOTHYROIDISM DURING PREGNANCY

When thyroid gland releases more less (underactive) thyroid hormones that condition is called Hypothyroidism. The prevalence of clinical hypothyroidism is 0.3–0.5% in pregnant women (Abalovich *et al*., 2007).

Types

Subclinical hypothyroidism, which is characterized by an elevated serum TSH with normal free thyroxine (FT4) and is observed in 3%–5% of women in pregnancy. (Reid *et al*., 2013).

Overt hypothyroidism, characterized by an elevated serum TSH and abnormal FT4 is observed in 0.3%–0.5% of women in pregnancy (Reid *et al*., 2013).

Causes

Hypothyroidism in women of reproductive age is most commonly caused by autoimmune thyroiditis, Hashimoto's disease (Abalovich *et al*., 2007). Other causes include prior radioactive iodine and/or surgical ablation of Graves' disease (GD) (Neale *et al*.,2004;Burrow *et al*.,2004)surgical removal of the thyroid because of multinodular goiter or thyroid cancer, overtreatment of hyperthyroidism with thionamides, medications that alter the absorption or metabolism of LT4, and central defects that inhibit the hypothalamic-pituitary-thyroid axis.

The fetal thyroid gland starts producing small amounts of thyroid hormone at approximately 10 weeks' gestation, until production plateaus at approximately 35 weeks. (Glinoer *et al*., 1990; Nayer *et al*., 1990)

Thus, particularly in the first trimester of pregnancy, the fetus depends entirely on thyroid hormone from the mother.

Complications

Maternal hypothyroidism can have devastating consequences if left untreated.

It is associated with:

- Spontaneous abortion (Abalovich et al., 2002; Gutierrez et al., 2002)
- Fetal death (Allan *et al*., 2000; Palomaki *et al*., 2000)

- Preterm delivery (Stagnaro-Green *et al*., 2009; Allan *et al*., 2000; Palomaki *et al*., 2000)
- Pregnancy induced hypertension (Leung *et al*., 1993. Millar *et al*.,1993)
- Gestational diabetes (Stagnaro-Green *et al*., 2009)
- Anemia,
- Postpartum hemorrhage. (Davis *et al*., 1998; Leveno *et al*., 1998)
- Placental abruption and preterm labor (Casey et al., 2005; Dashe *et al*., 2005)
- Preeclampsia (Ashoor *et al*., 2010; Rotas *et al*., 2010)
- Cesarean section (Cohen *et al*., 2010; Wiznitzer *et al*., 2010)
- Early embryo loss (De Vivo *et al*., 2010; Mancuso *et al*., 2010)
- Placental abruption
- Preterm labor (Casey *et al*., 2005; Dashe *et al*., 2005)
- Low birth weight
- Fetal distress
- Impaired neuropsychological development.
- Lower intelligence scores. (Haddow et al., 1999; Li et al., 2010; van den Boogaard *et al*., 2011).

Treatment

Treatment with levothyroxine is recommended and considered safe in pregnancy. (Abalovich *et al*., 2007).The goal of treatment is to maintain TSH within trimester-specific reference ranges:

0.1 to 2.5 mIU/L in the first trimester,

0.2 to 3.0 mIU/L in the second trimester, and

0.3 to 3.0 mIU/L in the third trimester. (Stagnaro-Green *et al*., 2011; Abalovich *et al*., 2011)

Thyroid function should be normalized as rapidly as possible after conception. TFTs ismeasured within 30 to 40 days of the first positive pregnancy test, and then every 4 to 6 weeks throughout pregnancy.

Physiological changes of Thyroid gland in pregnancy

Data from human and animal studies suggest that pregnancy alters normal thyroid function (Weetman *et al*., 2010). Thyroid physiology changes significantly during pregnancy. (Glinoer *et al*., 1997). During pregnancy, the thyroid gland increases in size by 10% in iodine replete countries, but by 20% to 40% in areas of iodine deficiency (ADA *et al*., 2014). The metabolic changes include:

1. Increase in Iodine Renal Clearance

During pregnancy, there is an enhanced urinary loss of iodine owing to an increased glomerular filtration rate, leading to iodine deficiency and maternal goiter (Banerjee *et al*., 2011).

2. The impact of Human Chorionic Gonadotrophin (HCG) on the Thyrotrope Receptor

Decrease in the level of thyroid-stimulating hormone (TSH) with an increase in pregnancy related hormone concentration- Human Chorionic Gonadotropin (Galofre et al., 2009).

3. An increase in serum Thyroxine-Binding Globulin (TBG)

There is an increase in thyroxine-binding globulin (TBG) because of elevated oestrogen a protein that transports thyroid hormone in the blood (Galofre et al., 2009).

4. Inner-ring Deiodination of Triiodothyronine (T3) and Thyroxine (T4) by the placenta

Placenta produces the enzyme type 3 deiodinase, which increases the peripheral metabolism of thyroid hormones and regulates the trans-placental transport of thyroid hormone and iodide (Landers *et al*., 2009).

A variety of endocrine disorders complicate pregnancy. Diabetes is the most prevalent and has been seen increasing prevalence of Diabetes in general and in young people in particular, which has led to increase in the number of Pregnancy with diabetes.

Gestational Diabetes Mellitus (GDM)

GDM is defined as glucose intolerance of varying degree with onset or first recognition during pregnancy. The prevalence of GDM in India varied from 3.8 to 21% in different parts of the country, depending on the geographical locations and diagnostic methods used. GDM has been found to be more prevalent in urban areas than in rural areas. The importance of GDM is that two generations are at risk of developing diabetes in the future. Women with a history of GDM are at increased risk of developing predominately type 2 diabetes and also their children. (Yogev *et al*., 2004)

Pathophysiology of GDM

GDM is closely associated with Diabetes mellitus type II, due to similarities in their many key pathophysiologic characteristics most importantly, insulin resistance. During pregnancy, woman develops insulin resistance, mainly due to hormone production. Some of these hormones are estrogen, cortisol, and human placental lactogen. These hormones can have a

blocking effect on insulin. This is called contra-insulin effect, which usually begins about 20 to 24 weeks in the pregnancy. As the placenta grows, more of these hormones are produced, and the risk of insulin resistance becomes greater. Normally, the pancreas is able to make additional insulin to overcome insulin resistance, but when the production of insulin is not enough to overcome the effect of the placental hormones, it results in gestational diabetes. **(**Poulakos *et al*., 2014).

Risk factors for Gestational Diabetes Mellitus

Although any woman can develop GDM during pregnancy, some of the factors that may increase the risk include the following (Chen P *et al*., 2015; Alfadhli *et al*., 2015)

- Overweight or obesity
- Family history of diabetes
- Having given birth previously to an infant weighing greater than 9 pounds
- Age (women age >25 are at a greater risk for developing gestational diabetes than younger women)
- Prediabetes, also known as impaired glucose tolerance

Adverse outcomes associated with GDM

Maternal (Wei *et al*., 2015; Alfadhli *et al*., 2015)

- Preeclampsia
- Women with a history of GDM have approximately a 30% likelihood of developing DM type 2 within 10 years
- Gestational hypertension

- Cesarean delivery
- Women with a history of GDM have up to a 60% likelihood of developing GDM in a future pregnancy

Fetal (Wei *et al*., 2015; Alfadhli *et al*., 2015)

- Shoulder dystocia/birth trauma
- Macrosomia
- Birth defects
- Hyperbilirubinemia
- Hypoglycemia

Treatment for GDM

First-line treatment for GDM is medical nutritional therapy, moderate exercise has been used in the management of GDM (ADA 2014).Pharmacotherapy is implemented when medical nutritional therapy and lifestyle measures fail. Insulin is the mainstay of pharmacotherapy. (ADA 2014).Insulin regimens can include intermediate and short acting insulin such as the regular recombinant insulin analogs aspart, lispro. Historically, insulin has been the drug of choice for the management of women with GDM.

Oral hypoglycemic agents such as glyburide (second generation sulfonylurea) and metformin (biguanide) are attractive alternatives to insulin due to lower cost, ease of administration, and better patient adherence. (Ryu *et al*., 2014).

Parameters

Thyroid function assessment

At the first antenatal visit (gestational age: 9–13 weeks), maternal serum samples were collected in 10 ml vacutainer tubes, centrifuged, and stored in aliquots at –80°C until assayed. Quantitative analyses of thyroid hormones [TSH] were performed using chemiluminescent microparticle immunoassays.

Oral Glucose Tolerance Test (OGTT)

The women were screened for Gestational Diabetes Mellitus (GDM) at 24–28 weeks and classified at that time as having GDM in the index pregnancy if any abnormal plasma glucose values were obtained during the 2 hours, 75g OGTT according to the Diabetes in Pregnancy Study Group India (DIPSI) diagnostic criteria.

Chapter 2

Literature Review

2. LITERATURE REVIEW

Thyroid disorders are one of the most common endocrine disorders in pregnancy. Thyroid disorders are known to be associated with abnormal maternal and fetal outcomes and are often overlooked in pregnant women because of nonspecific symptoms and hypermetabolic state of pregnancy.

Krajewski *et al.*, 2011 studied thyroid disorders in pregnancy and suggests that Normal thyroid function is essential in pregnancy to avoid complications in gestation and to ensure delivery, to the best extent possible, of a healthy baby. Women with hypothyroidism and (or) thyroid antibodies are at increased risk of miscarriage. Low thyroid hormone levels during pregnancy can have detrimental effects on the development of the fetal central nervous system and predispose to preterm delivery and spontaneous pregnancy loss.

Negro *et al.*, 2014 examined the peer-reviewed literature on hypothyroidism, hyperthyroidism and thyroid autoimmunity in pregnancy. Results suggests that overt hyperthyroidism and hypothyroidism are responsible for adverse obstetric and neonatal events. Thus concluded that overt hyperthyroidism and hypothyroidism need to be promptly treated and subclinical hypothyroidism also requires substitutive treatment.

Vissenberg *et al.*, 2012 conducted a systematic review which provides a comprehensive overview on the available treatment interventions on thyroid disorders before conception and in early pregnancy. Results suggests that for hyperthyroidism, methimazole and PTU are

effective in preventing pregnancy complications. For clinical hypothyroidism, treatment with levothyroxine is recommended. For subclinical hypothyroidism and thyroid autoimmunity, evidence is insufficient to recommend treatment with levothyroxine.

Jahagirdar *et al.*, 2012 evaluated Thyroid hormone role in regulating brain glucose metabolism and potentially modulating hippocampal cognitive processes. This review discusses evidence for mechanistic links between TH, insulin, cognitive function and brain glucose metabolism and reaches the conclusion that TH may modulate memory processes, likely at least in part by modulation of central insulin signaling and glucose metabolism.

Karakosta *et al.*, 2012 studied the association of thyroid function and autoimmunity in early pregnancy with adverse pregnancy and birth outcomes. The study used data from the prospective mother-child cohort "Rhea" study in Crete, Greece. A total of 1170 women with singleton pregnancies participated in this analysis. Maternal serum samples in the first trimester of pregnancy were tested for thyroid hormones (TSH, freeT4 and free T3) and thyroid antibodies (thyroid peroxidase antibody and thyroglobulin antibody). Outcomes included gestational diabetes, gestational hypertension/preeclampsia, cesarean section, preterm delivery, low birth weight. The combination of high TSH and thyroid autoimmunity in early pregnancy was associated with a 4-fold increased risk for gestational diabetes and a 3-fold increased risk for low birth weight neonates.

Stohl *et al.*, 2013 have evaluated if there is any connection between thyroid disease and gestational diabetes. They used retrospective data of all women with clinical thyroid disease

delivering at Johns Hopkins Hospital from January 2005 to December 2008. Clinical Parameters were abstracted and appropriate statistical tests were performed. Results states that GDM occurred in 12.3% of women in the study cohort. In hypothyroid women, 14.3% developed GDM compared to 5.8% of hyperthyroid women. If larger studies confirm the trends observed in this study, consideration should be given to including women with known thyroid disease in the subset of women who should be offered screening for diabetes early in pregnancy and appropriate clinical surveillance.

Shuai Yang *et al.*, 2016 have evaluated the correlations between different thyroid hormone levels in early pregnancy and the incidence of gestational diabetes mellitus. The study comprised 27,513motherswho provided early pregnancy serum samples for analyses of thyroid function. GDM was diagnosed using a 2 h, 75 g oral glucose tolerance test between 24-28weeks of gestation. The incidence of GDM in pregnant women tended to increase with age (5.83%, 10.18%, 14.95%, 22.40%, P<0.0001), increasing pre-pregnancy body mass index (BMI) (P<0.0001), a family history of diabetes (21.09% vs. 12.92%, P<0.0001).It was observed that the level of free T4 (FT4) in early pregnancy in GDM women was lower than that in non GDM women (P <0.0001). Increasing FT4 levels were associated with a protective effect against GDM thereby concluding that low thyroid hormone levels in early pregnancy are a risk factor for GDM incidence.

Tudela *et al.*, 2012 have evaluated if there is any relationship between subclinical thyroid disease and gestational diabetes between November 2000 and April 2003, serum thyrotropin screening was performed on all women who presented for prenatal care. Women with an

elevated serum thyrotropin but a normal serum free thyroxine were designated to have subclinical hypothyroidism and those with a low thyrotropin and a normal serum free thyroxine level were designated to have subclinical hyperthyroidism. Euthyroid women had both normal thyrotropin and normal serum free thyroxine values. The incidence of gestational diabetes was compared among these three groups. Of the 24,883 women included in the study, 23,771 (95.5%) were Euthyroid, 584 (2.3%) had subclinical hyperthyroidism and 528 (2%) had subclinical hypothyroidism. The risk of developing gestational diabetes increased with thyrotropin level. There by supporting a relationship between subclinical hypothyroidism and diabetes diagnosed during pregnancy.

Das Bishnu Prasad *et al*., 2015 have studied the relationship between gestational diabetes mellitus with hypothyroidism in pregnancy between June 2014 and May 2015.They had 2 groups of patients 100 in each group, Euthyroid group (control) and hypothyroid (study) group. Grouping was done based on the serum thyrotropin (TSH) levels, normal thyrotropin values were taken as 0.2 to 3mIU/L as per American Thyroid Association guidelines. Patients from both the groups were subjected to oral glucose tolerance test with 75gm oral glucose according to DIPSI guidelines. The incidence of gestational diabetes mellitus was compared between the study and the control group Gestational diabetes was more in the hypothyroid group (8%) than in the control group (1%), (P= 0.0349).The risk of developing gestational diabetes increases with hypothyroidism. This supports a relationship between hypothyroidism and diabetes, diagnosed during pregnancy.

Li-Li Gong *et al*., 2015 conducted a meta-analysis to investigate whether hypothyroidism in Pregnancy is associated with gestational diabetes risk. They searched the published literature from PubMed and EMBASE. Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using a fixed- or random-effects model. Seven articles described the relationship between hypothyroidism and risk of gestational diabetes. This meta-analysis revealed that overt hypothyroidism was associated with an increased risk of gestational diabetes (OR 1.892, 95% CI 1.679e2.132, $p < 0.001$). The relative risk of gestational diabetes was also increased in subclinical hypothyroidism, with the OR of 1.558 (95% CI 1.292e1.877, $p < 0.001$).There was no evidence of significant association between hypothyroxinemia and risk of gestational diabetes (OR 1.394, 95% CI 0.753e2.580, p ¼ 0.291). The OR for all of the hypothyroidism was 1.749 (95%) CI 1.586e1.928, $p < 0.001$), and an association was found.

Chapter 3

Aim & Objective

3. AIM AND OBJECTIVE

- To investigate the association between thyroid dysfunction in pregnancy and risk of developing gestational diabetes mellitus.
- To identify the other risk factors for developing gestational diabetes mellitus.

Chapter 4

Plan of Study

4. PLAN OF STUDY

PHASE- I (3 months):

- Preliminary literature survey
- Protocol preparation

PHASE – II (6 months):

- Obtaining approval from Institutional Human Ethical Committee
- Allocation of cases
- Data collection

PHASE – III (3 months):

- Data interpretation
- Statistics
- Results
- Discussion

Chapter 5

Materials & Methods

5. MATERIALS AND METHODS

STUDY TYPE

Observational

STUDY DESIGN

Prospective

STUDY CENTER

Department of Endocrinology, Obstetrics & Gynaecology, PSG IMS&R

Coimbatore. It is a multi-speciality 900 bedded tertiary care hospital located in the southern part of Tamilnadu.

STUDY POPULATION

Pregnant Women

SAMPLE SIZE

204 patients

STUDY DURATION

1year

STUDY PERIOD

November 2016 to July2017

INCLUSIVE CRITERIA

- Pregnant women with Age > 18 yrs

EXCLUSIVE CRITERIA

- Cases with Diabetes mellitus (Type -1 or Type -2) diagnosed prior to pregnancy
- Pregnancy with more than one foetus

- Chronic medical conditions such as HIV/AIDS, kidney disease, SLE and Autoimmune diseases

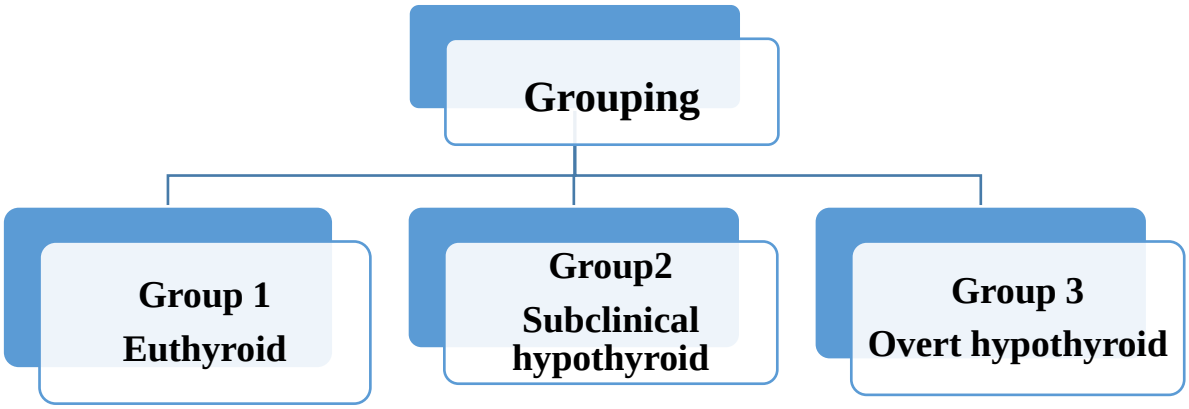
STUDY TOOLS:

Patient Data Collection Form

STUDY APPROVAL:

The approval for the study was obtained from Institutional Human Ethical Committee (IHEC), PSGIMSR. Project No: 16/438.

GROUPING



STUDY PROCEDURE:

- The study protocol was prepared and submitted to the Institutional Human Ethical Committee (IHEC) for approval.
- The protocol was approved by IHEC.
- This was then informed and the permit was obtained from the Heads of Departments, Obstetrics&Gynecologyand Endocrinology, PSG Hospitals, Coimbatore.

- The study was commenced in the outpatient Departments of Obstetrics&Gynecology and Endocrinology, PSG Hospitals, Coimbatore.
- All the pregnant women above18 years, present for antenatal care, were explained about the study protocol in the language understandable to them (English, Tamil).
- Written informed consent was obtained from thepatients who agreed and were enrolled in the study.
- Demographic details such as age, BMI,occupation, contact information and all the data concerning their medical history was obtained.
- Study participants were screened for Serum Thyrotropin levels (TSH, FT4) during their first trimester (9 -13 weeks)based on which they were grouped (Table -1),cut off values were obtained from 'AMERICAN THYROID ASSOCIATION'2017 (Table -2)and were followed up until their second trimester
- Between (24-28weeks) they were subjected to oral glucose tolerance test according to DIPSI guidelines for GDM diagnosis.

DIAGNOSIS OF GDM

Diabetes in pregnancy study group India (DIPSI) diagnostic criteria,diagnosed based on the 2 – hour 75gm oral glucose tolerance test (OGTT) with a threshold plasma glucose concentration greater than 140 mg/ dl at 2 hour, performed in fasting /non –fasting state irrespective of the last meal timing.

Table 1. TSH cut off values according to American thyroid association guidelines

GROUPS	TSH VALUES	PATIENT CONDITION
GROUP -1	0.1-2.5mU/L	EUTHYROID
GROUP-2	>2.5mU/L	SUBCLINICAL HYPOTHYROID
GROUP-3	>10mU/L	OVERT HYPOTHYROID

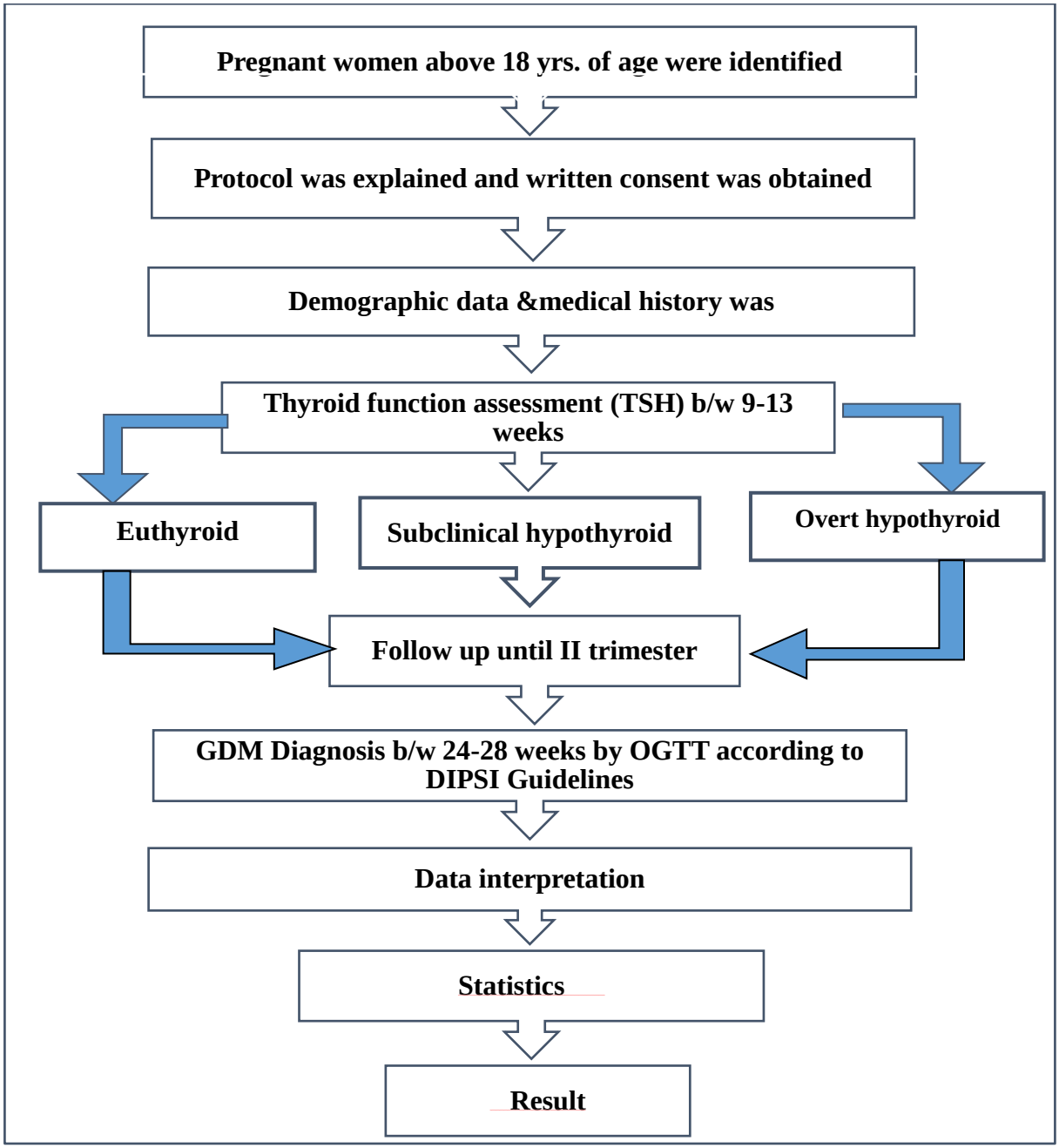
Table 2. TSH reference values in different trimesters.

GESTATIONAL AGE	TSH REFERENCE VALUES
FIRST TRIMESTER	0.1 – 2.5mU/L
SECOND TRIMESTER	0.2 – 3.0mU/L
THIRD TRIMESTER	0.3 – 3.0mU/L

STATISTICAL ANALYSIS

Data were analyzed using the Statistical package for social sciences (IBM SPSS, version 19). Incidence of GDM with the demographic factors and clinical characteristicswere assessed by ANOVA andstudent's t-test. Group wise correlation between the clinical characteristics and GDM were assessed by Pearson's x^2 test. GDM risk analysis between the groups were assessed by odds ratio (OR), and exact 95% confidence intervals (CI). P values <0.5 were considered as statistically significant.

STUDY PROCEDURE (flow chart)



Chapter 6

Results

6. RESULTS

Table 3. Demographic data of the study population.

DEMOGRAPHICS		EUTHYROID	SUBCLINICAL HYPO-THYROID	OVERT HYPO-THYROID
Total Patients n (%)		100(49.02)	78(38.23)	26(12.75)
Age	± SD	25.6±3.9	26.5± 4.4	25.3±3.5
	< 25 n (%)	43(43)	27(34.6)	11(42.3)
	25-29 n (%)	39(39)	29(37.1)	10(38.46)
	30-34 n (%)	15(15)	17(21.7)	5(19.23)
	≥35 n (%)	3(3)	5(6.14)	0
BMI pre-pregnancy(kg/ $m^{2)}$	±SD	24.4± 4.1	25.1± 4.3	26.4± 3.2
	Underweight n (%)	9(9)	2(2.56)	-
	Normal weight n (%)	40(40)	29(37.94)	6(23.07)
	Overweight n (%)	34(34)	34(43.5)	14(53.84)
	Obese n (%)	17(17)	13(16.66)	6(23.07)
Occupation n (%)	working	14(14)	16(20.5)	7(26.9)
	House wife	86(86)	62(79.48)	19(73.7)
Family History of Diabetes n (%)		18(18)	25(32.05)	8(30.76)
History of GDM n (%)		3(3)	4(5.12)	1(3.86)
History of PCOD n (%)		6(6)	4(5.12)	2(7.69)
History of Thyroid n (%)		1(1)	17(21.79)	4(15.38)
History of Infertility n (%)		3(3)	3(3.84)	4(15.38)

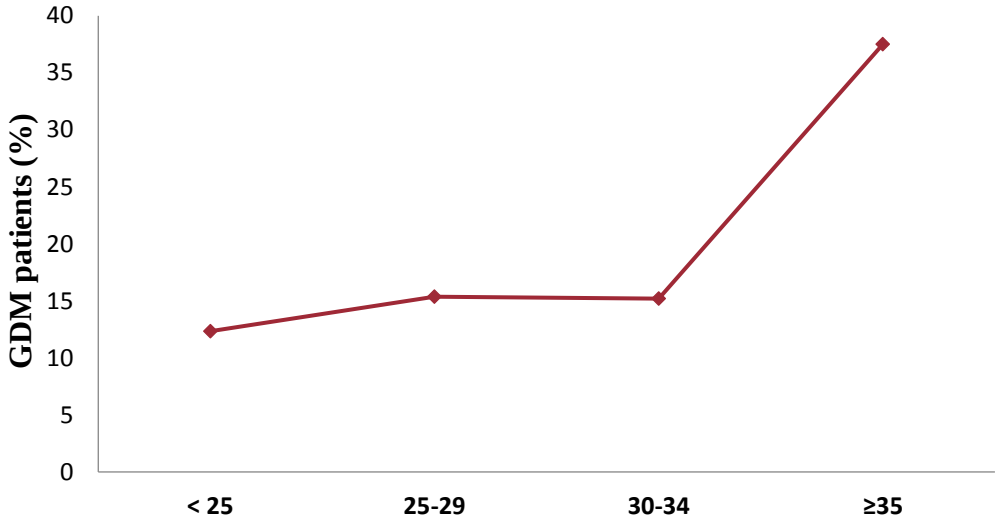
n- Number of patients
(%) – Percentage

Table 4. Comparison of the Demographic Factors across the study population

Demographic Factors		Number of Patients (%)	No. of GDM patients (%)	P values
Age	< 25	81 (39.7%)	10(12.34%)	0.2053
	25-29	78(38.2%)	12(15.38%)	
	30-34	37(18.1%)	6(16.21%)	
	≥35	8(3.92%)	3(37.5%)	
BMI pre-pregnancy (kg/m^2)	Underweight	11(5.39%)	1 (9.09%)	0.0738
	Normal weight	75 (36.76%)	9 (12%)	
	Overweight	82 (40.19%)	14(17.07%)	
	Obesity	36 (17.64%)	6 (16.66%)	
Occupation	working	37 (18.13%)	6(1.62%)	0.2877
	House wife	167(81.86%)	24 (14.3%)	

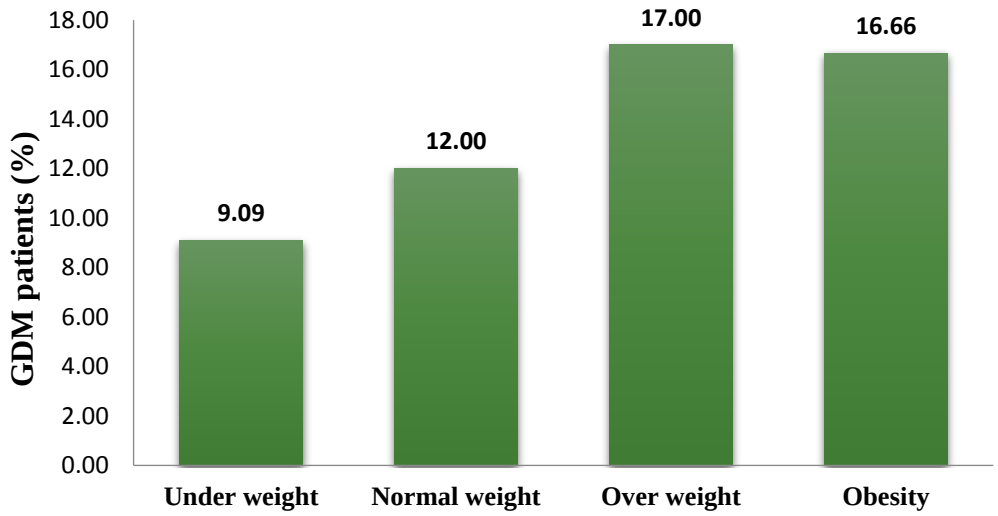
Data was analyzed using ANOVA (analysis of variance) and Student's t test, P values <0.5 were considered as statistically significant.

Fig. No. 1: Incidence of GDM in different age group patients



39.75%of study population were in the age group <25yrs out of which 12.34% had developed GDM. 38.2% of the study population were between the age group 25 to 29 out of which15.38% had developed GDM.18.1% of the study population were between the age group 30 to 34 out of which 16.21% developed GDM. 3.92% of the study population were of the age ≥35 out of which 37.5%developed GDM.

Fig. No. 2: Incidence of GDM in patients with different BMI



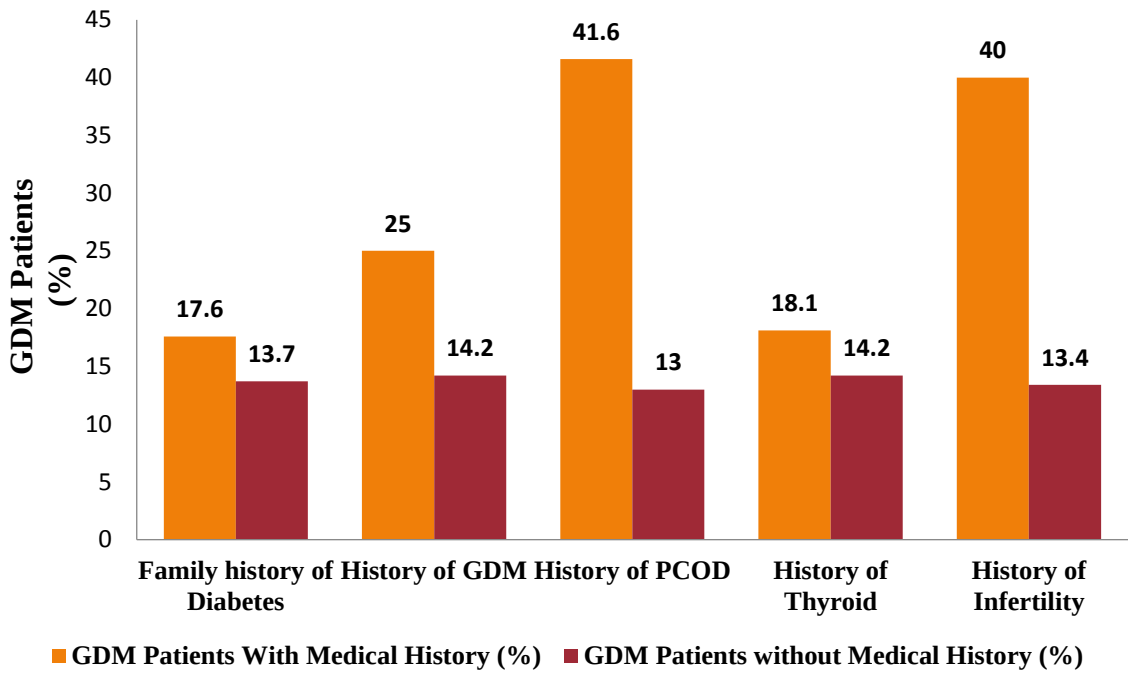
5.39% of the study population who were underweight had 9.09% incidence of GDM. 36.9% of the study population who were normal weight had 12% incidence of GDM.40.19%of the study population who were overweight had 17.07% incidence of GDM. 17.64% of the study population who were obese had 16.66% incidence of GDM.

Table 5. Comparison of the clinical characteristics across the study population.

Clinical characteristics	Total Number of Patients (%)		No. of GDM Patients (%)		P values
	With	Without	With	Without	
Family history of Diabetes	51(24.5%)	153(75%)	9(17.6%)	21(13.7%)	0.257
History of GDM	8(3.9%)	196(96%)	2(25%)	28(14.2%)	0.280
History of PCOD	12(5.8%)	192(94.1%)	5(41.6%)	25(13%)	**0.037***
History of Thyroid	22(10.7%)	182(89.2%)	4(18.1%)	26(14.2%)	0.589
History of Infertility	10(4.9%)	194(95%)	4 (40%)	26(13.4%)	**0.003*****

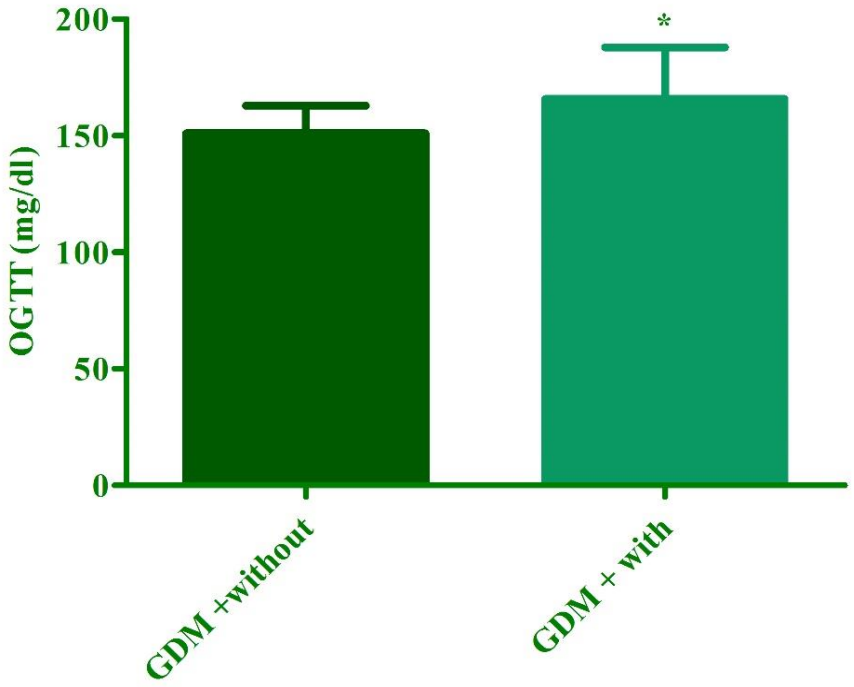
Data was analyzed using Student's t test, P values <0.5 were considered as statistically significant.

Fig. No. 3: Incidence ofGDM in patients with and without medical history



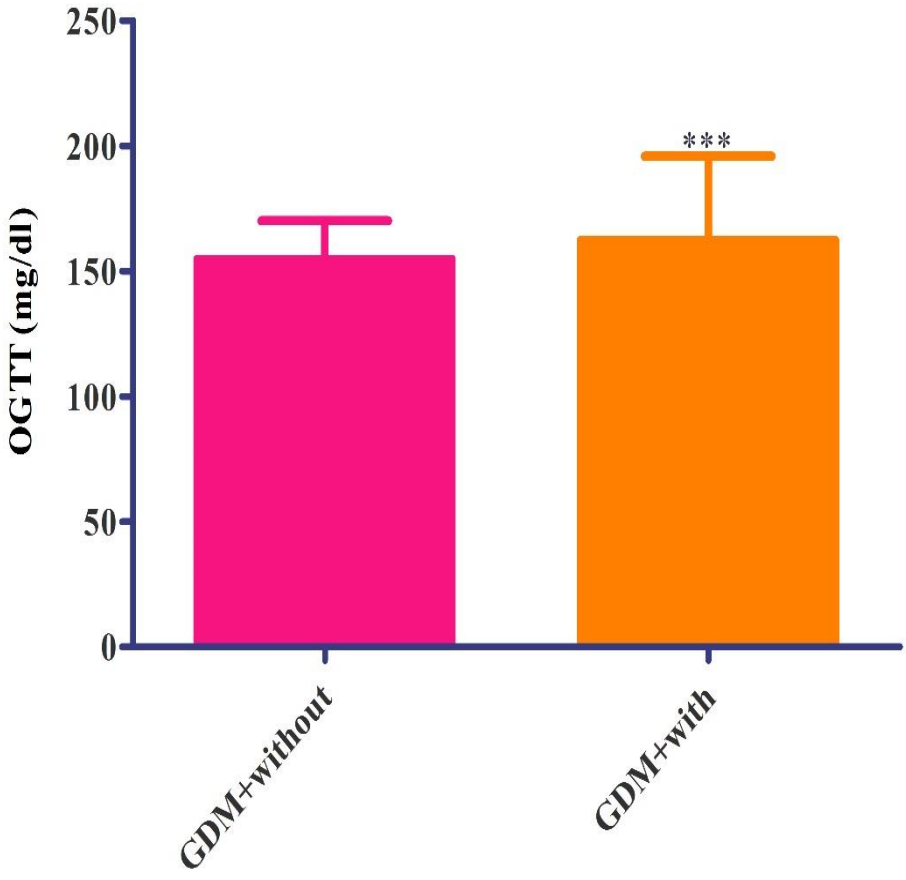
There was a slight increase in the incidence of GDM in patients who are having a family history of diabetes when compared with those without family history of diabetes (17.67% vs.13.7%), in patients with history of thyroid than those without history of thyroid (18.1% vs. 14.2%), in patients with history of GDM when compared with those without (25% vs. 14.2%).There was significant increase in the incidence of GDM in patients who are having a history of PCOD when compared with those without history of PCOD (41.6% vs. 13%) and in patients with history of infertility than those without history of infertility (40% vs. 13.4%)

Fig. No. 4: Incidence of GDM in patients with and without History of PCOD



Data are expressed as mean ±SD. Statistical analysis was carried out using Student's t test.* denotes statistical significance of pregnant women with a family history of PCOD having higher incidence of GDM than those without family history of PCOD (41.6% vs. 13%, p =0.037, *P* <.05).

Fig. No. 5: Incidence of GDM in patients with and without History of Infertility



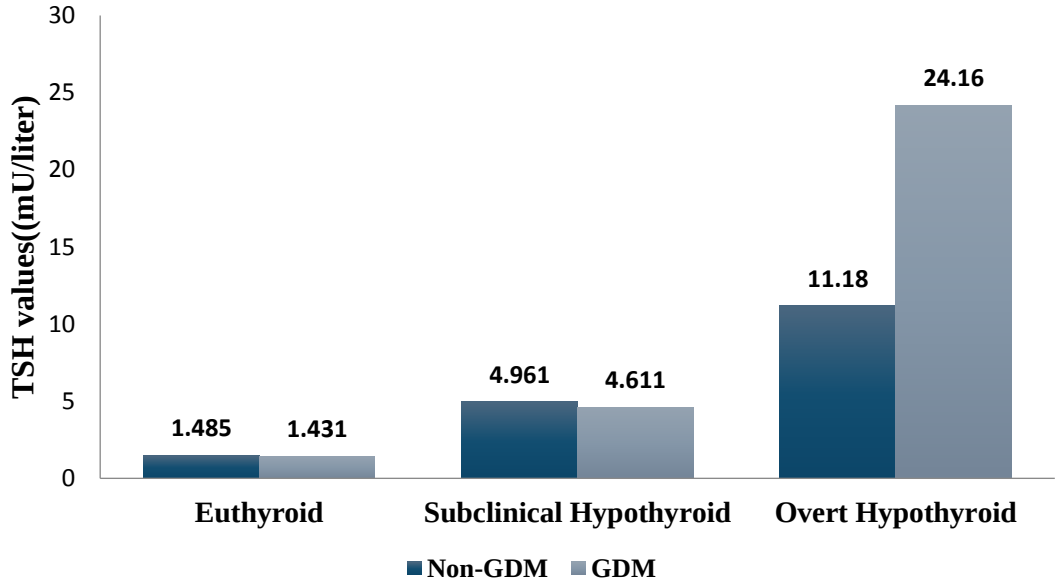
Data are expressed as mean ±SD. Statistical analysis was carried out using Student's t test. *** denotes statistical significance of Pregnant women with a family history of infertility having much higher incidence of GDM than those without family history of infertility (40% vs. 13.4%, p =0.001, *P* <.001).

Table 6. Comparison of Thyrotropin (TSH) values in early pregnancy between GDM and non-GDM pregnant women

Patients	TSH values((mU/liter)		P value
	Non-GDM	GDM	
Total Patients	3.662 (n=174)	7.299 (n=30)	**0.0358***
Euthyroid	1.485 (n=89)	1.431 (n=11)	0.8022
Subclinical Hypothyroid	4.961 (n=32)	4.611 (n=14)	0.5584
Overt Hypothyroid	11.18 (n=19)	24.16 (n=5)	**0.0145***

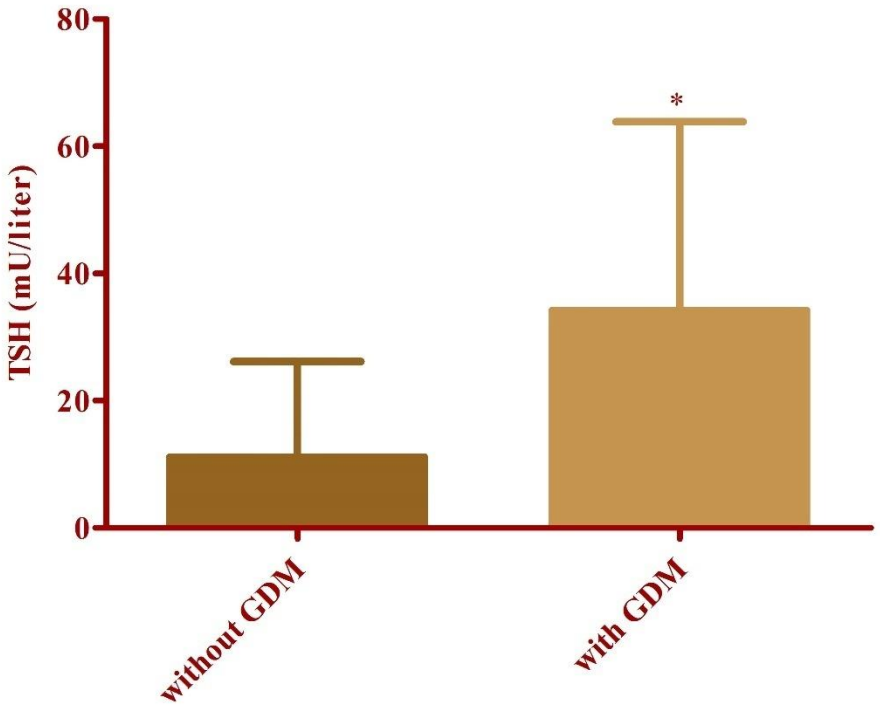
Data was analyzed using Student's t test, P values <0.5 were considered as statistically Significant.

Fig. No. 6: comparison of mean TSH values between GDM and non GDM patients.



In Euthyroid group mean TSH values slightly decreased in GDM patients when compared with and non GDM patients (1.431mU/liter vs.1.485mU/liter). In subclinical hypothyroid group mean TSH values slightly decreased in GDM patients when compared to non GDM patients (4.611mU/liter vs. 4.961mU/liter). In Overt hypothyroid group mean TSH values increased in GDM patients when compared with non GDM patients (24.16mU/liter vs. 11.18mU/liter).

Fig. No. 7: comparison of mean TSH values inovert hypothyroid group between GDM and non GDM patients



Data are expressed as mean ±SD. Statistical analysis was carried out using Student's t test. * denotes statistical significance ofmean serum TSH in overt hypothyroid patients with GDM when compared with non GDM patients within the same group (24.6mU/liter vs. 11.18mU/liter, p=0.014).

Table 7. Comparison of OGTT values in GDM patients.

OGTT Values	Euthyroid	Subclinical Hypothyroid	Overt Hypothyroid
≥140	144.8(n=11)	149.6(n=14)	169.2(n=5)
P value		0.0617	**< 0.001*** **

Fig. No. 8: Mean OGTT values of GDM patients in different group

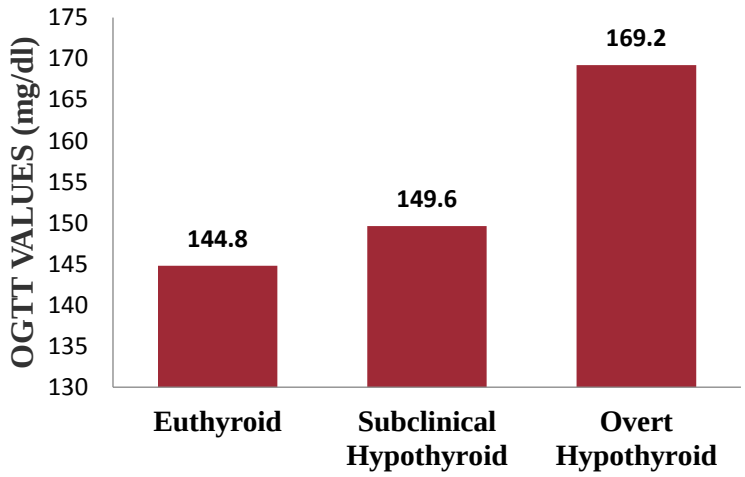
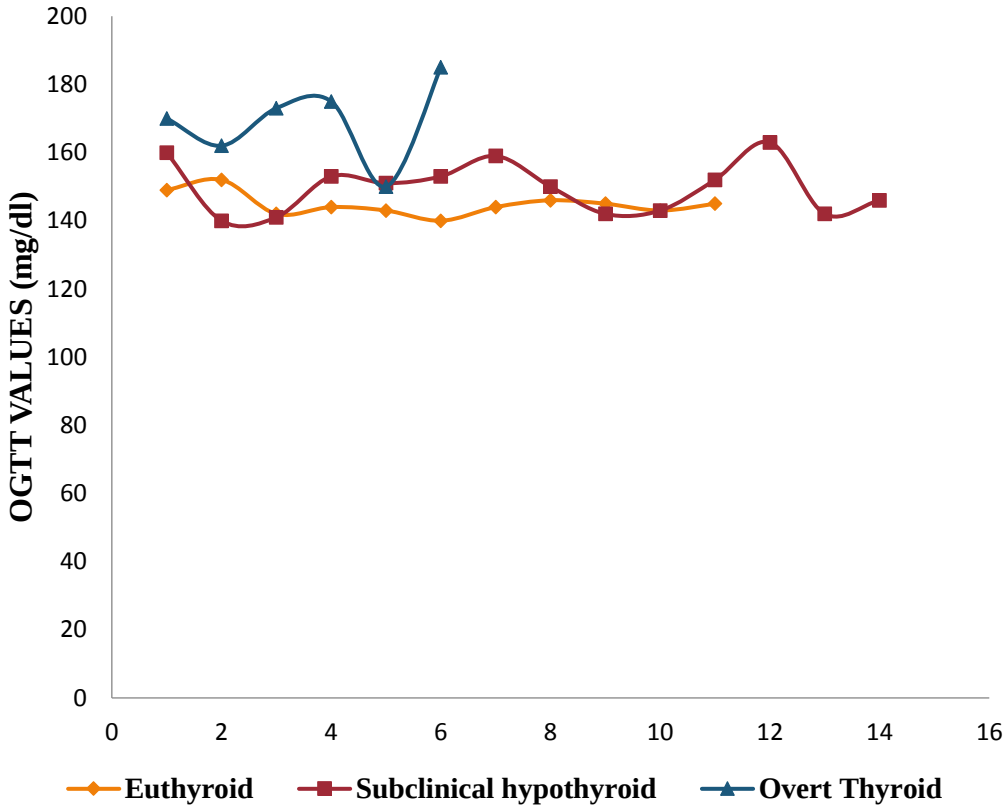
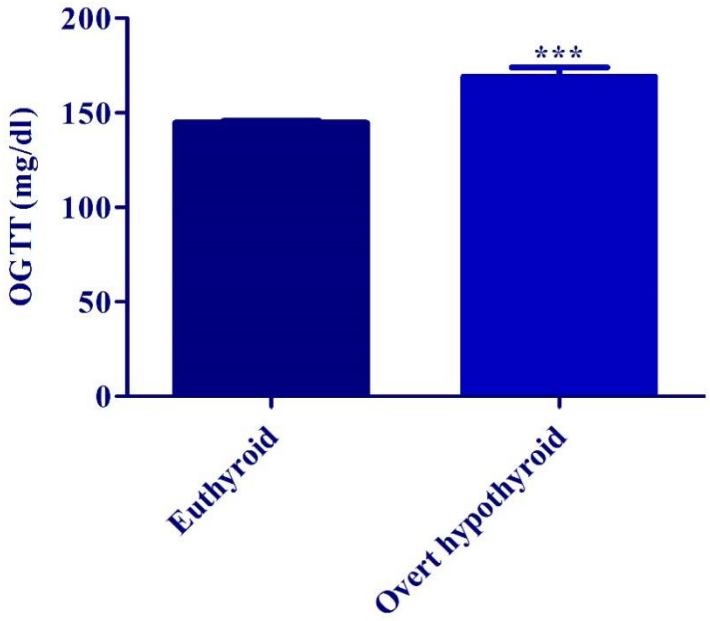


Fig. No. 9: OGTT values of GDM patients in different groups



The OGTT values of GDM patients are shown in the above graph. OGTT values of euthyroid patients are in the range between 140mg/dl to 152mg/dl, in subclinically hypothyroid patients the values are in between 140mg/dl to 160mg/dl and in overthypothyroid patients the values ranging between 150mg/dl to 185

Fig. No.10: Mean OGTT values Euthyroid vs overt hypothyroid group



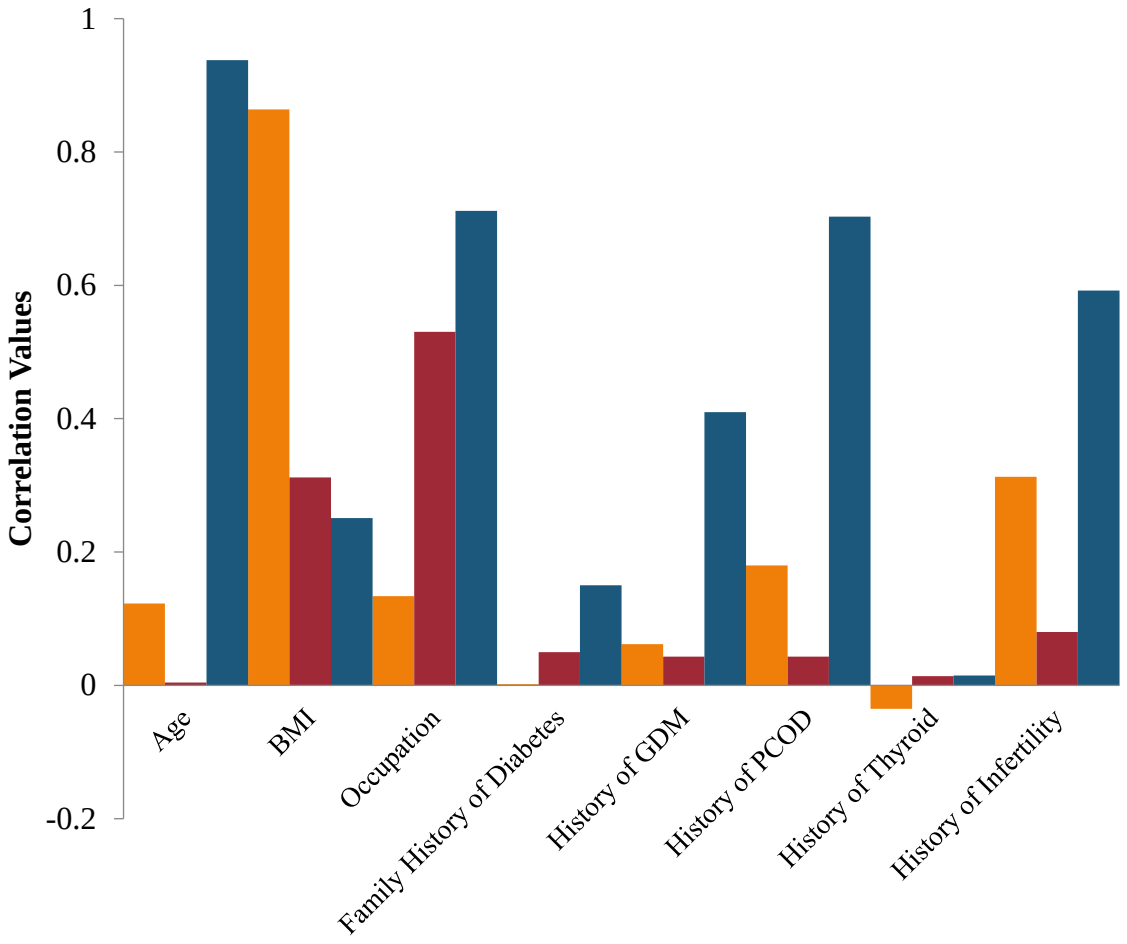
Data are expressed as mean ±SD. Statistical analysis was carried out using Student's t test. *** denotes statistical significance of mean OGTT values inovert hypothyroid group when compared with Euthyroid group (144.8mg/dl vs. 16.2 mg/dl, P< 0.001)

Table 8. Group wise Correlation of clinical characteristics with GDM using Pearson correlation analysis.

Clinical characteristics	Correlation values		
	Euthyroid	**Subclinical hypothyroid**	**Overt Hypothyroid**
Age	0.123	**0.0042***	0.9378
BMI	0.864	0.3118	0.2509
Occupation	0.134	0.5303	0.7115
Family History of Diabetes	0.002	0.050	0.150
History of GDM	0.062	0.043	**0.410***
History of PCOD	0.180	0.043	**0.703****
History of Thyroid	-0.035	0.014	0.015
History of Infertility	**0.313****	0.080	**0.592****

Correlation analysis was performed using Pearson's x^2 test.

Fig. No. 11: Group wise Correlation of clinical characteristics with GDM using Pearson correlation analysis.



In Euthyroid group there is a positive correlation between history of infertility and GDM (0.313).In subclinical hypothyroid group there is a positive correlation between age and GDM (0.004).In overt Hypothyroid group there is a positive correlation between history of GDM and GDM (0.410), history of PCOD and GDM (0.703), history of infertility and GDM (0.592).

Table 9. GDM risk analysis using Odds ratio

Odd Ratios	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for group (Euthyroid / subclinical)	1.770	0.755	4.151
Odds Ratio for group (Euthyroid / overt hypothyroid)	1.926	0.604	6.140

Subclinical hypothyroid group has 1.7 times more risk for developing gestational diabetes mellitus when compared with Euthyroid group. Overt hypothyroid group has 1.9 times more risk for developing gestational diabetes mellitus when compared with Euthyroid group.

Chapter 7

Discussion

7. DISCUSSION

The studies exploring the association between thyroid dysfunction and gestational diabetes are comparatively less in the Indian population, the incidence of gestational diabetes mellitus (GDM) in pregnant women with thyroid disorders is less clear, so the aim of this observational, prospective study was to investigate the association between thyroid dysfunction and risk of developing gestational diabetes mellitus.

(Das Bishnu Prasad *et al*., 2015) reported that, the risk of developing gestational diabetes increases with thyrotropin level. Similar findings were reflected in the present study where, the incidence of GDM was found to be increased in subclinical hypothyroid and overt hypothyroid groups when compared with Euthyroid group (17.94% vs. 11%), (19.23 vs. 11%).Interesting finding was, overt hypothyroid patients with GDM had higher levels of mean serum TSH in their early pregnancy when compared with non GDM patients within the same group (24.6 mU/liter vs. 11.18mU/liter).The proposed reason for the above findings is as follows, thyroid hormones play an important role in glucose metabolism. Triiodothyronine (T3) is the biologically active hormone that is primarily responsible for glucose metabolic activity(Pisarev *et al*.,2010) and 80% of circulating T3 is converted peripherally via deiodinase activity and the monodeiodination of T4 (Haddow *et al.*,2016).Studies have shown that several mechanisms are involved in the thyroid hormone-mediated regulation of glucose metabolism. This can be explained by the following: a) Reduce the half-life of insulin, accelerate the rate at which insulin is degraded, and increase the release of the inactive precursors of insulin; b) Promote hepatic glucose output by increasing the expression of glucose transporter 2 (GLUT2) in liver cell membranes and c) Activate β -adrenergic

receptors via CAMP, which increases the sensitivity of catecholamines, powerful hormones that accelerate glycogenolysis (Das *et al*., 1984).

Studies have also shown that many of the pathways between the hypothalamic- pituitary axis and the T3 receptor in thyroid cells are abnormal in patients with diabetes (Yang *et al*., 2016). Pregnancies complicated with thyroid disorders especially, in hypothyroidism there is an increased chance of impaired glucose tolerance (Das Bishnu Prasad *et al*., 2015). Similar results were obtained in the present study where, oral glucose tolerant test (OGTT) mean values of GDM patients were significantly high in overt hypothyroid patients (169.2mg/dl) when compared with Euthyroid patients (144.8mg/dl). The proposed reason for the above findings is that patients with either hypothyroidism or subclinical hypothyroidism can exhibit insulin resistance. In vivo and in vitro studies have shown that this resistance may be caused by a reduced need for insulin or glucose utilization in peripheral tissues that have been damaged by insulin (Maratou *et al*., 2009).

In the present study39.75%of study population were in the age group <25yrs out of which 12.34% had developed GDM. 38.2% of the study population were between the age group 25 to 29 out of which15.38% had developed GDM.18.1% of the study population were between the age group 30 to 34 out of which 16.21%developed GDM.3.92% of the study population were of the age ≥35 out of which 37.5%developed GDM. We found that, the incidence of GDM increased with increase in maternal age, our findings were in agreement with the previous studies who (Khalil *et al*., 2013) reported that incidence of GDM increases with maternal age reaching a plateau at around 40 years.

The reason for the above findings could be explained by the: i) association between aging and progressive vascular endothelial damage, ii) decreased insulin sensitivity with age and in individuals with impaired glucose tolerance (Fulop *et al*., 2003), iii) pancreatic ß cell function falls with age (Szoke *et al*., 2008).

(Yang *et al*., 2016) reported that the incidence rate of GDM has gradually increased as pre pregnancy BMI has increased. Similar results were obtained in the present study where 5.39% of the study population who were underweight had 9.09% incidence of GDM. 36.9% of the study population who were normal weight had 12% incidence of GDM.40.19%of the study population who were overweight had 17.07% incidence of GDM.17.64%of the study population who were obese had 16.66% incidence of GDM. The proposed reasons for increased GDM with increased pre pregnancy BMI are, in over weight and obese women insulin resistance is increased. The combination of obesity and insulin resistance increases the long-term risk of these individuals developing metabolic dysregulation in pregnancy, i.e. gestational diabetes (Catalano *et al*., 2010).

Endocrine, inflammatory and neuronal pathways link obesity to insulin resistance.

a) The obesity-associated increase in Fatty acids (FAs) can trigger insulin resistance through intracellular metabolites that activate protein kinase C (PKC), leading to the activation of serine/threonine kinases that inhibit insulin signaling. b) Obesity-associated changes in secretion of adipokines that modulate insulin signaling. c) Obesity-associated inflammatory factors. Obesity is characterized by an increase in the accumulation of adipose tissue macrophages (ATMs), which increase the adipose tissue production of inflammatory cytokines that inhibit insulin signaling. d) Endocrine and inflammatory mediators converging

on serine/threonine kinases that inhibit insulin signaling. e) Obesity-associated activation of NF-κB heightens inflammatory responses that exacerbate insulin resistance. f) suppressor of cytokine signaling (SOCS) family proteins, induced by adipokines, induce insulin resistance either by interfering with IRS-1 and IRS-2 tyrosine phosphorylation or by targeting IRS-1 and IRS-2 for proteosomal degradation. g) FAs also trigger insulin resistance by direct activation of TLR4 (toll like receptor) and the innate immune response. h) Obesity-related alteration in the central response to hormonal and nutrient signals alters peripheral insulin sensitivity (Qatanani *et al*., 2007).

From the study results obtained, we found that, incidence of GDM increased with family history of diabetes, history of thyroid, history of GDM when compared with those patients without family history of diabetes, history of thyroid, history of GDM (17.6% vs 13.7%), (18.1% vs 14.2%) & (25% vs 14.2%) respectively. The obtained results are not statistically significant, the reason might be a small sample size.

In the present study we observed that, incidence of GDM was higher in patients with history of PCOD than those without history of PCOD (41.6% vs. 13.4%, p =0.037). The observed results are in consistent with the earlier reports (Jun *et al*., 2013) which states that Women with PCOD are at increased risk for developing GDM. Mechanisms that might explain an increased risk of GDM with history of PCOD are related to Insulin resistance which is believed to play an intrinsic role in the pathogenesis of PCOD (Dunaif *et al*., 1995) reported that, increased insulin receptor serine phosphorylation decreases its protein tyrosine kinase activity resulting in the post-binding defect in insulin action which is characteristic of PCOD.

Incidence of GDM was higher in patients with history of infertility than those without history of infertility (40.6% vs. 13.4%, p = 0.003). The observed results are in consistent with the earlier reports (Tobias *et al*., 2013) which suggested that infertility is associated with an increased risk of developing gestational diabetes mellitus. (Holst *et al*., 2016) mechanisms that might explain an increased risk of GDM after fertility problems are probably related to the underlying cause of infertility, the procedures involved in the treatment of infertility, or both (Ashrafi *et al*.,2014). Regarding the underlying fertility problems, it has been suggested that the association with risk of GDM is primarily attributable to PCOD. PCOD has been shown to increase the risk of GDM, possibly owing to a high prevalence of insulin resistance in these women (Boomsma *et al*., 2006). Regarding the mechanisms associated with fertility treatment, researchers have argued that the hormonal environment induced during ART or ovulation induction may explain or contribute to the development of GDM (Maman *et al*., 1998). For instance, the hormone progesterone, which is commonly used in fertility treatment (for luteal-phase support) has been suggested to have a diabetogenic effect in pregnancy, possibly by increasing insulin resistance in skeletal muscle and adipose tissue. Thus, it is biologically plausible that factors related to both the underlying fertility problem and fertility treatment increase the risk of GDM.

(Stohl *et al*., 2013) reported that women with hypothyroidism had more incidence of GDM when compared to women with hyperthyroidism. These findings are in contrast to the study by (Sahu *et al*., 2009) who demonstrated an association between hyperthyroidism and the development of GDM. In the present study we could not enroll patients with hyperthyroidism as its prevalence is very less.

Chapter 8

Summary & Conclusion

8. SUMMARY AND CONCLUSION

In our present study we investigated the association between thyroid dysfunction and increased risk of developing gestational diabetes mellitus and assessed the other risk factors for developing gestational diabetes mellitus.

- We found that, incidence of GDM is high in overt hypothyroid groups when compared with other groups.
- Oral glucose tolerant test (OGTT) mean values of GDM patients were significantly high in overt hypothyroid patients when compared with Euthyroid patients.
- Interesting finding was that, overt hypothyroid patients with GDM had significantly high mean serum TSH values in their early pregnancy when compared to overt hypothyroid patients without GDM thereby indicating the association between thyroid dysfunction in pregnancy and gestational diabetes mellitus.
- Incidence of GDM increased with increase in age, BMI, family history of diabetes, history of GDM, history of thyroid but dint reach the statistical significance
- Patients with history of PCOD and history of infertility had significantly higher incidence of GDM.

CONCLUSION

The present study can be concluded that, thyroid dysfunction especially overt hypothyroidism is associated with increased risk of developing gestational diabetes mellitus. History of PCOD and history of infertility are the notable risk factors for developing GDM.

It is prudent to identify women with thyroid dysfunction at the earliest in order to detect gestational diabetes mellitus with least delay and treat with vigilance. However, a long term study covering a wide spectrum of patients is likely to provide a better knowledge in understanding the relationship between thyroid dysfunction and increased risk of developing gestational diabetes.

Future Outlook

FUTURE OUTLOOK

This study can be continued in future by following up the women with Gestational diabetes mellitus to find out the Obstetric outcomes such as Delivery method and likelihood of developing DM type 2

Post-delivery neonatal outcomes such as Shoulder dystocia/ birth trauma, Macrosomia, Birth defects, Hyperbilirubinemia, Hypoglycemia

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Annexures

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

To
Ms K Sirisha
II Year M Pharm
Guide/s: Dr R Senthil Kumar / Dr Seetha Panicker / Mr G Venkatesh
PSG College of Pharmacy
Coimbatore 641 004

Ref: Project No.16/438

Date: January 23, 2017

Dear Ms Sirisha,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 30.12.2016 to conduct the research study entitled "*Thyroid dysfunction and increased risk of developing gestational diabetes mellitus*" during the IHEC meeting held on 13.01.2017.

The following documents were reviewed and approved:

1. Project submission form
2. Study protocol (Version 1 dated 30.12.2016)
3. Informed consent forms (Version 2 dated 20.01.2017)
4. Data collection tool (Version 1 dated 30.12.2016)
5. Permission letter from concerned Heads of Department
6. Current CVs of Principal investigator, Co-investigator
7. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 13.01.2017 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr R Nandakumar (Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr S Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Dr D Vijaya	M Sc., Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
   d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
   e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
   f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

SECRETARY
PSG IMS&R
COIMBATORE-641004
INSTITUTIONAL HUMAN ETHICS

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee

பூ. சா. கோ மருத்துவக் கல்லூரி மற்றும் ஆராய்ச்சி நிறுவனம், கோவை

மனித நெறிமுறைக் குழு

ஒப்புதல் படிவம்

தேதி:

சிரிஷ்மா .கா, ஆகிய நான் பூ. சா. கோ மருத்துவக் கல்லூரியின் / மருத்துவமனையின் மருந்தாக்கவியல் துறையின் கீழ், **"தைராய்டு மற்றும் கர்ப்பகால நீரிழிவு நோய் தாக்கம் அதிகரிக்கிறதா"** என்ற தலைப்பில் ஆய்வு மேற்கொள்ள உள்ளேன்.

என் ஆய்வு வழிகாட்டி: G. வெங்கடேஷ்

ஆய்வு மேற்கொள்வதற்கான அடிப்படை:

தைராய்டு மற்றும் கர்ப்பகால நீரிழிவு நோய் தாக்கம் அதிகரிக்கிறதா என்பதைப் பற்றிய விழிப்புணர்வு நோயாளிகளிடையே குறைவாக இருப்பதனால் அதனை மேம்படுத்துவதற்காக இந்த ஆய்வு மேற்கொள்ளப்படுகிறது.

ஆய்வின் நோக்கம்:

- தைராய்டு மற்றும் கர்ப்பகால நீரிழிவு நோய் தாக்கம் அதிகரிக்கிறதா என்பதைப் பற்றி சோதனை செய்தல்.

ஆய்வில் பங்கு பெறும் நபர்களின் எண்ணிக்கை: 264

ஆய்வில் பங்கு பெறுவோர் மற்றும் வயது: 18 வயதிற்கு மேற்பட்ட கர்ப்பகால நீரிழிவு நோய் உள்ளவர்கள்.

ஆய்வு மேற்கொள்ளும் இடம்: மகப்பேறு மருத்துவத் துறை, பூ. சா. கோ மருத்துவமனை, கோயம்புத்தூர்.

இந்த ஆய்வில் எங்களுடன் ஒத்துழைக்குமாறு கேட்டுக்கொள்கிறோம். நாங்கள் சில தகவல்களை இந்த ஆய்விற்காக சேகரிக்க உள்ளோம்.

ஆய்வு செய்யப்படும் முறை:

முதன்மை நேர்காணல்: 10 நிமிடங்கள்

இந்த ஆய்வில் கிடைக்கும் தகவல்கள் **3 வருடங்கள்** பாதுகாக்கப்படும். இந்த தகவல்கள் வேறு ஆய்விற்குப் பயன்படுத்தப் படும்/பயன்படுத்தப் பட மாட்டாது.

சுகாதாரக் கல்வி: அமர்வுகள்: ___ முறை ஒரு அமர்வுக்கான நேரம்: ___ நிமிடங்கள் **பொருந்தாது**

மருத்துவ பரிசோதனைகள்:

இரத்த மாதிரி சேகரிப்பு: _____ மிலி _____ முறை **பொருந்தாது**

இரத்த மாதிரி எடுப்பது வழக்கமான சிகிச்சைக்காகவோ அல்லது இந்த ஆய்விற்காகவோ:

பொருந்தாது

இதனால் ஏற்படக் கூடிய அசௌகரியங்கள் / பக்க விளைவுகள்: பொருந்தாது

இரத்த மாதிரிகள் ஆய்விற்குப் பின் பாதுகாத்து வைக்கப்படுமா? ஆம் / இல்லை, அழிக்கப்படும்: **பொருந்தாது**

சேகரிக்கப்பட்ட இரத்தம் விற்கப்படுமா? ஆம் / இல்லை **பொருந்தாது**

சேகரிக்கப்பட்ட இரத்தம் வேறு நிறுவனத்துடன் பகிர்ந்து கொள்ளப்படுமா? ஆம் / இல்லை: **பொருந்தாது**

மருந்துகள் ஏதேனும் கொடுக்கப்படவிருந்தால் அவை பற்றிய விவரம் (கொடுக்கப்படும் காரணம், காலம், பக்க விளைவுகள், பயன்கள்): **பொருந்தாது**

மருந்துகள் கொடுக்கப்படுவது வழக்கமான சிகிச்சை முறையா?: ஆம் / இல்லை (இல்லை என்றால் கொடுக்கப்படும் காரணம்) **பொருந்தாது**

கொடுக்கப்படும் மருந்துகளுக்கு மாற்று உள்ளதா?: ஆம் / இல்லை (ஆம் என்றால் இந்த குறிப்பிட்ட மருந்து கொடுக்கப்படும் காரணம்) **பொருந்தாது**

ஆய்வில் பங்குபெறுவதால் ஏற்படும் பலன்கள்:
தைராய்டு மற்றும் கர்ப்பகால நீரிழிவு நோய் தாக்கம் அதிகரிக்கிறதா என்பதைப் பற்றிய விழிப்புணர்வு நோயாளிகளிடையே மேம்படும் மற்றும் நோயின் தீவிரம் அதிகம் உள்ளவர்களுக்கு உதவுகிறது.

ஆய்வினால் ஏற்படக் கூடிய அசௌகரியங்கள் / பக்க விளைவுகள்: இதனால் எந்த அசௌகரியமோ, பக்க விளைவுகளோ ஏற்படாது.

ஆய்வின் முடிவுகள் எந்த முறையில் பயன்படுத்தப்படும்?
தைராய்டு மற்றும் கர்ப்பகால நீரிழிவு நோய் தாக்கம் அதிகரிக்கிறதா என்பதை அறிய பயன்படுத்தப்படும்.

இந்த ஆய்வின் மூலம், அவர்களுடைய கருவாய் வாய் புற்றுநோயினைப் பற்றிய அறிவுத்திறனை மதிப்பீடு செய்து, போதுமான ஆலோசனைகளை வழங்கி, அவர்களையும், அவர்களை சார்ந்து உள்ளவர்களையும் கருவாய் வாய் புற்றுநோயிலிருந்து பாதுகாத்தல்.

இந்த ஆய்வின் கேள்விகளுக்கு பதிலளிப்பதோ, இரத்த மாதிரிகள் அல்லது திசு மாதிரிகள் எடுப்பதிலோ உங்களுக்கு ஏதேனும் அசௌகரியங்கள் இருந்தால், எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு. ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சை முறையில் எந்த வித பாதிப்பும் இருக்காது என்று உங்களுக்கு உறுதியளிக்கிறோம். மருத்துவ மனையில் நோயாளிகளுக்கு அளிக்கப்படும் சேவைகளை நீங்கள் தொடர்ந்து பெறலாம். இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொள்ளுவதால் வேறு எந்த விதமான கூடுதலான பலனும் உங்களுக்குக் கிடைக்காது. நீங்கள் அளிக்கும் தகவல்கள் இரகசியமாக வைக்கப்படும். ஆய்வில் பங்கேற்பவர்கள் பற்றியோ அவர்கள் குடும்பத்தைப் பற்றியோ எந்தத் தகவலும் எக்காரணம் கொண்டும் வெளியிடப்படாது என்று உறுதியளிக்கிறோம். நீங்கள் அளிக்கும் தகவல்கள் / இரத்த மாதிரிகள் / திசு மாதிரிகள் அங்கீகரிக்கப்பட்ட ஆய்விற்கு மட்டுமே பயன்படுத்தப்படும். இந்த ஆய்வு நடைபெறும் காலத்தில் குறிப்பிடத்தகுந்த புதிய கண்டுபிடிப்புகள் அல்லது பக்க விளைவுகள் ஏதும் ஏற்பட்டால் உங்களுக்குத் தெரிவிக்கப்படும். இதனால் ஆய்வில் தொடர்ந்து பங்கு பெறுவது பற்றிய உங்கள் நிலைப்பாட்டை நீங்கள் தெரிவிக்க ஏதுவாகும்.

ஆய்வுக்குட்படுபவரின் ஒப்புதல்: இந்த ஆய்வைப் பற்றிய மேற்கூறிய தகவல்களை நான் படித்து அறிந்து கொண்டேன் / ஆய்வாளர் படிக்கக் கேட்டுத் தெரிந்து கொண்டேன். ஆய்வினைப் பற்றி நன்றாகப் புரிந்து கொண்டு இந்த ஆய்வில் பங்கு பெற ஒப்புக்கொள்கிறேன். இந்த ஆய்வில் பங்கேற்பதற்கான எனது ஒப்புதலை கீழே கையொப்பமிட்டு. கை ரேகை பதித்து நான் தெரிவித்துக் கொள்கிறேன்.

பங்கேற்பாளரின் பெயர், முகவரி:

பங்கேற்பாளரின் கையொப்பம் / கை ரேகை / சட்டப்பூர்வ பிரதிநிதியின் கையொப்பம்:

தேதி :

ஆய்வாளரின் கையொப்பம்:
தேதி :

ஆய்வாளரின் தொலைபேசி எண்: 9620971916
மனித நெறிமுறைக் குழு அலுவலகத்தின் தொலைபேசி எண்:
அலுவலக நேரத்தில் 0422 2570170 Extn.: 5818

PATIENT PROFORMA

Patient name:

Ip/op no:

Diagnosis:

Occupation:

Age:

BMI:

Family history of Diabetes mellitus:

Previous history of GDM:

Past History of Thyroid:

History of PCOD:

History of Infertility:

Physical Exercise:

Other Complications :

INVESTIGATIONS

TSH VALUES:

OGTT VALUES:

Study Volunteer ID:
Study Volunteer Name:

PSG Institute of Medical Science and Research, Coimbatore
Institutional Human Ethics Committee
INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS

(strike off items that are not applicable)

1. I / We (write name of the investigator(s) here), **K.SIRISHA** am / are carrying out a study on the topic: **Thyroid dysfunction and increased risk of developing gestational diabetes mellitus** as part of my / our research project being carried out under the aegis of the Department of: Pharmacology

(*Applicable to students only*): My / our research guide is: Mr. G.Venkatesh, M. Pharm.,

The justification for this study is: There is a need for a prospective study covering a wide spectrum of patients to provide a better knowledge in understanding the association of thyroid dysfunction and increased risk of developing gestational diabetes mellitus.

The objectives of this study are:

: To investigate the association between Thyroid dysfunction in pregnancy and risk of developing Gestational diabetes mellitus.

Sample size: 264

Study volunteers / participants are (specify population group & age group): pregnant women › 18 years.

Location: Department of obstetrics& Gynaecology, PSG Hospital, Coimbatore

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out:

Initial interview (specify approximate duration): 10 minutes.

Data collected will be stored for a period of 3 years. We will / will not use the data as part of another study.

Health education sessions: Number of sessions: **-NA-** Approximate **duration** of each session:

-NA- minutes.

Clinical examination (Specify details and purpose):

Blood sample collection: Specify quantity of blood being drawn: **- NA-** ml.

No. of times it will be collected: **NA-.**

Whether blood sample collection is part of routine procedure or for research (study) purpose:

Study Volunteer ID:
Study Volunteer Name:

1. Routine procedure 2. Research purpose

Specify **purpose**, discomfort likely to be felt and side effects, if any: **-NA-**

Whether blood sample collected will be stored after study period: Yes / No, it will be destroyed

Whether blood sample collected will be sold: Yes / No

Whether blood sample collected will be shared with persons from another institution: Yes / No

Medication given, if any, duration, side effects, purpose, benefits:

Whether medication given is part of routine procedure: Yes / No (If not, state reasons for giving this medication)

Whether alternatives are available for medication given: Yes / No (If not, state reasons for giving this particular medication)

Final interview (specify approximate duration): **-NA-** mts. If **photograph** is taken, purpose:

Benefits from this study: knowledge regarding the association of Thyroid dysfunction and increased risk of developing gestational diabetes mellitus (GDM) will be established.

This study will be helpful in identifying the pregnant women with increased risk of developing GDM

Risks involved by participating in this study: **NIL**

How the **results** will be used: To identify the pregnant women with increased risk of developing gestational diabetes mellitus

If you are uncomfortable in answering any of our questions during the course of the interview / biological sample collection, **you have the right to withdraw from the interview / study at anytime.** You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only. You will be informed about any significant new findings - including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature / Left thumb impression of the Study Volunteer / Legal Representative:

Study Volunteer ID:
Study Volunteer Name:

Signature of the Interviewer with date: Witness:

Contact number of PI:9620971916

Contact number of Ethics Committee Office: 0422 4345818

PSG COLLEGE OF PHARMACY, COIMBATORE

WORKSHOP ON

ROLE OF PHARMACIST IN CLINICAL RESEARCH

Certificate of Participation

This is to certify that Dr. / Mr. / Ms. Sirisha Kamaraju

has participated as delegate in one day workshop sponsored by **Novartis Healthcare Pvt Ltd, Hyderabad** *on 24th June 2016 held at PSG College of Pharmacy, Coimbatore*

Mr. Santosh Shevade
Program Coordinator
Novartis Healthcare Pvt Ltd

Dr. M. Ramanathan
Principal
PSG College of Pharmacy

PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH

COIMBATORE - 641 004

CME Accreditation Certificate

This is to certify that Sirisha

has participated in

MOLECULAR BASIS OF MALIGNANCY - CURRENT TRENDS

held at PSG IMS&R on 23-06-2016 as a participant

This activity has been reviewed and accepted by The Centre for Accreditation, The Tamil Nadu Dr. MGR Medical University and the University designates this educational activity for a maximum of 05 Credit points in Category 1

Moderator

Dr. S. Ramalingam
Dean